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Using spray-dried lactose monohydrate in wet granulation method for a low-dose oral formulation of a paliperidone derivative

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ABSTRACT

Content uniformity (CU) is a crucial evaluation factor, especially for low-dose oral formulations. Spray-dried monohydrate lactose is generally recommended for direct compression/dry granulation, but we observed that it showed advantages in the wet granulation tableting method for low-dose tablet formulation. In this study, several commercial brands of lactose were selected and suitable tableting methods were applied to a low-dose oral formulation of pentyloxyl paliperidone derivative (PD6) with drug loading at 1.5% (w/w) and lower. The effects of spray-dried/sieved/milled monohydrate and anhydrous lactose on CU were investigated. Granules/powder mixtures were studied in terms of their size distribution, repose angle, flowability and bulk/tapped density. In addition, SEM, DSC, CU, tablet weight, hardness, friability and *in vitro* cumulative release profiles were investigated. The relationships between the powder characteristics and CU results were also studied. Wet granules using spray-dried lactose monohydrate presented satisfied flowability, fair compressibility and a low particle size span compared with all the other tested types of lactose. The product tablets also presented optimal evaluation results for 1.5% (w/w) drug loading (CU = 12.22) and displayed good repeatability among 100 g to 2 kg levels. Further study using another two brands of lactose produced similar results, indicating using spray-dried monohydrate lactose in wet granulation may apply universally to low-dose formulations.

1. Introduction

Paliperidone was launched by Johnson and Johnson under the trade name of Invega® at the end of 2006 to treat schizophrenia. The poor absolute oral bioavailability (only 28%) and high daily dose may lead to an increased risk of side effects and thus inhibit its effectiveness. A series of paliperidone derivatives (PDs) were synthesised in our lab. Among these derivatives, pentyloxyl paliperidone hydrochloride (PD6) displayed higher bioavailability and lower toxicity in animal experiments than Invega®. The chemical structure and physico-chemical properties are shown in Fig. 1 and Table 1. Due to the nearly doubled bioavailability of PD6, a low-dose oral formulation was needed [1].

Content uniformity (CU, or the uniformity of dosage unit, defined as the degree of uniformity in the amount of the active substance in each unit) may be the most important evaluation factor of oral solid preparations. CU testing of dosage units is conducted throughout different phases of pharmaceutical research and development to ensure the consistency of dosage units regarding the content of the active pharmaceutical ingredient (API, the substance in a pharmaceutical drug or a pesticide that is biologically active; this can be substituted for drug in certain cases). Numerous methods have been invented and developed to conduct this testing. Methods that generally sample a certain amount of tablets from lots/batches and novel means, such as near-infrared spectroscopy [2], have also been developed, but their limitation is the time-consuming work required for making a standard model for each different API. In addition, predication models have been established to estimate the outcome CU results via excipient characteristics but are limited in their requirement of similar tablet weight and/or excipient size distribution [3]. These limitations make the models unable to properly apply to low-dose formulation because the overwhelming majority of powder mixtures involve different types of excipients.

With respect to low-dose formulation, in the 1970s, the British Pharmacopoeia described low-dose formulation as "containing less than 2 mg or 2% drug loading (w/w) of active pharmaceutical ingredients (API)" [4,5], whereas U.S. standards limit the API to less than 1%[6]. Over the last few decades, the pharmaceutical industry has discovered and developed many low-dose drug products. In most cases, these products were in the form of tablet. However, low-dose tablet manufacturing remains a very challenging task due to the (1) difficulty in achieving CU, which is the most important evaluation factor; (2) low potency due to manufacturing loss and (3) instability due

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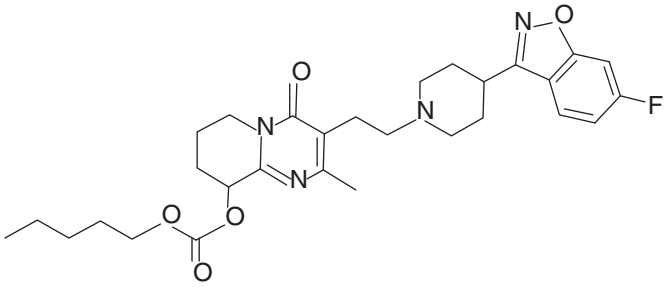

Fig. 1. Chemical structure of PD6.

to the huge ratio of excipients to drug substance and thus a lack of compatibility [7,8]. To obtain better CU results for low-dose tablets, manufacturing methods have been studied, and some advances have been made in various aspects [7–14].

For those drugs that have already been approved, complicated formulation design and miscellaneous excipients were used. Some excipients have been particularly noted for usage in low-dose oral formulation, such as spray-dried lactose [15] and CAB-O-SIL [16]. The excipient's (solid powder/particles in most cases) engineering, characterisation, and modelling of particles are three obviously important issues with respect to achieving a deeper understanding of structure–function–performance relationships of pharmaceutical products [17]. It should be noted that these recommended low-dose oral formulation excipients are nearly all emphasised in terms of the function of improving the flowability of the whole mixed materials. However, the interactions between the API and excipients are extremely complex. Some mechanisms have been used to describe the potential effect of excipients on API, but such interactions must still be evaluated on a case-by-case basis [18]. Numerous commercially available excipients have been developed and improved to meet different needs. For instance, for lactose, which is commonly used as a filler and diluent in oral solid formulations, the products vary in secondary processing methods (sieved, milled, spray-dried, etc.) and therefore present different characteristics, such as degrees of fines, particle size and surface morphology. These manufacturing variances are intended to meet the demands of different products and facilitate the task of formulation design. As for the lactose usage guidelines for tablets, sieved α-lactose monohydrate is recommend in direct compression, whereas milled α-lactose monohydrate is strongly suggested in wet granulation. Alternatively, spray-dried monohydrate lactose, which consists of spherical agglomerates of crystalline lactose monohydrate in a matrix of amorphous lactose, is considered to be "free-flowing" and is typically used in direct compression. Due to its brittle nature and lack of crystal water, anhydrous lactose could meet the needs of moisture-sensitive API formulations in dry granulation and direct compression. For different tableting methods, the interactions among the excipients differ both in the physical and chemical respects. External power in processing, i.e., wetting agent in wet granulation and slugging in dry granulation, can greatly alter the properties of the outcome mixed materials eventually affect the tablet evaluation results.

The mentioned research, development of excipients, manufacturing methods and instruments are all intended to achieve materials with a good flow property. The flowability of materials has an impact on nearly all pharmaceutical handling processes, such as blending, transfer, storage, feed and compaction. During all of the processing steps, an ideal even distribution of the API among all excipients is expected. Several evaluation parameters (repose angle, Carr index and Hausner ratio, etc.) of the particles/powder mixture can be used as references for predicting the outcome results as being acceptable or unacceptable [19]. In total, the mixtures of API and excipients need to present not only a small particle distribution span (minimising the segregation and agglomeration) but also good flowability (easy re-dispersion after storing) and good compactability for achieving tablets with small weight variations. In addition, when considering the later processing steps, such as film coating, a smooth surface and certain hardness are required for the product tablets.

Table 1
Physical and chemical properties of PD6 and paliperidone.

Drug	Mw	Melting point (°C)	Solubility in water (mg/ml)
PD6	577.09	225.40–226.60	2.09
Paliperidone	426.48	166.00–172.00	0.22

In our former study, we observed that for a drug loading as low as a 1.5% (w/w, 3 mg dosage strength) tablet formulation with lactose monohydrate, tablets manufactured using dry granulation presented much better tablet CU results than tablets manufactured using wet granulation [1]. However, serious powder pollution (especially for this low-dose oral formulation) and drug loss in the dry granulation (and direct compression) process are not acceptable for actual production. Therefore, the wet granulation method became the only choice, and the amelioration of the CU issue is required. However, due to the long $T_{1/2}$ of PD6 [20], a steady but rapid *in vitro* drug release profile must be achieved. The intent of this study was to find a suitable low-dose formulation using the wet granulation method to produce a tablet with satisfactory evaluation results. After initial exploration and pre-experimentation, a simple formulation was designed: drug 1.5%, HPMC 15% and lactose 83.5% (w/w). Five commercially available lactose products of the same brand (DMV-Frontier) were selected: D 11SD, D 110M, D 125M, D 200M, and D 21AN. Their characteristics are presented in Table 2. Wet granulation, dry granulation, as well as direct compression were adopted.

The repose angle, flowability, bulk and tapped density of the granules/powder were studied. DSC and SEM were conducted to determine the thermal and morphology properties. The cumulative release profiles were documented and fitted with a zero-order equation, a first-order equation, a Higuchi equation, and a Korsmeyer Peppas equation. The most important value, CU, was tested, and tablet weight, hardness and friability properties were also studied. The most suitable form of lactose was selected for lower dosage strength formulations of 1.5 mg (drug loading 0.75% (w/w) and 0.75 mg (drug loading 0.375% w/w), with batch sizes of 500 g and 1 kg.

2. Materials and methods

2.1. Materials

The drug PD6 was synthesised in our lab; 70% ethanol was used as the wetting agent, and the drug was prepared just before use. All other chemicals used were of analytical grade. Deionised water was prepared by purifying using a Milli-Q system (Millipore, Milford, USA).

The excipients used were as follows: magnesium stearate (Sinopharm Chemical Reagent Co., Ltd.) as a lubricant in the tableting process, HPMC K 100LV CR (Lot.PD 355155, Methocel® K100 PremiumLV CR) (The Dow Chemical Company) as a gel-forming matrix material and lactose (detailed information shown in Table 2) as a filler/diluent for achieving the desired tablet weight. The types/brands/batch lot information of lactose were as follows: SuperTab 11SD (Lot. 10587945), SuperTab 21AN (Lot. 10323925), Pharmatose 110 M(Lot.10693215), Pharmatose 125M(Lot.10420314) and Pharmatose 200 M (Lot. 10430981) (DEVELING INTERNATIONAL); FlowLac® 100 (LOT-NO:L 1125 A 4952) and Granulac® 200 (LOT-NO: L1015 A 4172) (MEGGLE Group Wasserburg Representative Office, Shanghai); and Foremost NF Lactose Hydrate Monohydrate Spray Dry Fast Flo 316 (BATCH NO. 8510943147) and Foremost NF Lactose Monohydrate 314WG (BATCH NO.8511042814) (Beijing Fengli Jingqiu commerce and Trade Co., Carbon double-sided Tape, Ltd.). All of the excipients were kept in desiccators at ambient temperature and used directly out of the desiccators.

Table 2
Properties of lactose and recommendation for using in tablet manufacturing method[a].

Lactose	DMV-Fonterra				
Type	Pharmatose 110M	Pharmatose 125M	Pharmatose 200M	SuperTab 11SD	SuperTab 21AN
Kind	Lactose monohydrate (sieved)	Lactose monohydrate (sieved)	Lactose monohydrate (milled)	Spray-dried lactose (sieved)	Lactose anhydrous (sieved)
Recommend for	Dry granulation; direct compression; powder mixing	Wet granulation	Wet and dry granulation	Usual direct compression formulation; low dose formulation	Usual direct compression formulation; water-sensitive API; chew tablet; high dose drug loading

[a] Digested from an official pamphlet and sample info.

2.2. Methods

2.2.1. Batch design and pre-mixing

The drug PD6 (milled in advance) and other excipients were weighed with an electronic analytical balance with an accuracy of 1:10,000 (Sartorius Scientific Instruments (Beijing) Co., Ltd.) according to the formulation design and batch size of 100 g. Three parallel batches were reproduced using different added lactose. The mixture was then poured into a SYH-5 3-dimension blender (Nanjing Fang'ou Machinery Equipment Co., Ltd.) and mixed for 15 min. The outcome powder mixture was processed with three tableting methods (wet granulation, dry granulation and direct compress method). D 11SD and wet granulation were used for 1.5-mg and 0.75-mg dosage strength tablet manufacture. The proportion of the drug plus lactose remained the same, and the drug loading was 0.75% for the 1.5-mg tablet and 0.375% for the 0.75-mg tablet. The proportions of lactose were 84.25% and 84.625%, respectively. The batch size was set to 100 g, 500 g and 1 kg levels.

2.2.2. Granulation method

For the wet granulation process, the powder mixture was transferred into a JB-10L propeller blender (Jiangsu Taixing Pharmaceutical Machinery No. 2 Factory, China), pre-blended for 5 min, and 700 mL of 70% ethanol was sprayed evenly onto the mixture. The wetting time was controlled to be approximately 10 min to 15 min. The soft material was then transferred to a Pharmag WG-30 (Pharma Test Apparatebau, Hainburg, Germany), and a 1.00-mm sieving attachment was used in the granulating process. The material was granulated at 90 rpm for 15 min. The granules were collected and dried at 45 °C in a DHG-9140A electric heating air-blowing drier (Shanghai Yiheng Scientific Instruments Co., Ltd.) for 45 min with intermittent stirring. For the dry granulation process, the powder mixture was dry granulated with a GL2-25 dry granulator (Kai Chuang Mechanical Manufacturing Co., Ltd., Jiangsu, China), and the parameters were the following: 6–8 Hz for the feeding rate, 8–10 Hz for the moulding rate, and 15–20 Hz for the granulation rate. In addition, a 1.00-mm sieve and 1.7-mm sieve were used for the upper and lower sieve, respectively.

2.2.3. Tableting

During the process, 1% (w/w) magnesium stearate was used as a lubricant and mixed with a granule/powder mixture in a blender for 15 min. The tableting process was conducted with a ZP-8 rotary tablet press (Shanghai Tianxiang & Chentai Pharmaceutical Machinery Co., Ltd.) with the power output set to 40 kN. The tablets had a cylindrical shape. For different lactose batches, 3 parallel batches were tableted separately, and the product tablets were put together for further testament.

2.2.4. Characterisation of granules/powder mixture

Granule/powder mixture samples for evaluation experiments were sampled by at least 5 withdrawals (each time 10 ml volume from 3 parallel batches) from random parts of the whole mixtures immediately following the granulation/mixing step, and the samples were continuously until just before the following evaluations were conducted.

The repose angle and flowability were tested with a PTG-S4 Powder Characterisation Instrument (PHARMA TEST Apparatebau AG, Hainburg, Germany). For the repose angle test, at least 45 g of the granule/powder mixture was used. For the flowability test, at least 100 g of the granule/powder mixture was used. The nozzle outlet diameters were 6 mm, 8 mm and 10 mm for the repose angle test, and 10 mm, 15 mm and 20 mm for the flowability test. The paddle speed and appropriate diameter nozzles were chosen based on if the granule/powder mixture flow state was acceptable and had good reproducibility. Each result was obtained from the average of three measurements.

Bulk and tapped density test was conducting using a PT-TD200 Tapping Density and Apparent Volume Tester (PHARMA TEST Apparatebau AG, Hainburg, Germany). A 100-ml volume of powder or particles was used. The initial weight was recorded. After vibrating 1250 times, the powder or particle volume was again recorded. The Carr index (C) and Hausner Ratio (H) were calculated based on the initial density and final density [21].

Particle analysis was conducted with the LS 13320 mW powder system Laser Diffraction Particle Size Analyzer (BECKMAN COULTER). The granule/powder mixture was tested for particle size distribution using a dry powder dispersing system and a sample volume of 15 ml.

Differential Scan Calorimetry was conducted with a DSC 1 STAR® System (METTLER TOLEDO, USA). A standard 40-μL aluminium pan with a centrally located pin and a pinhole on the lid was used as the sample holder for an approximately 10-mg sample loading. In addition, 150 ml/min of nitrogen was used as the protect gas, and the segment gas was nitrogen set to 30 ml/min for the granule/powder mixture sample and 50 ml/min for the HPMC K100LV CR. The temperature was set as 25 °C–400 °C for the tablet samples and 40 °C–150 °C for the HPMC K100LV CR [22]. The heating rate was 10 K/min for all of the experiments. STARe Evaluation software was used for the results analysis.

Scanning electron microscopy (SEM) analysis was conducted with a JSM-6700F Field Emission Scanning Electron Microscope (JEOL Ltd., Tokyo, Japan) to obtain a visual image and to evaluate the particle size, shape, and surface. The samples were affixed to the sample holder with carbon double-sided tape, and the excess portion was blown off with a rubber suction bulb.

2.2.5. The evaluation of tablet characteristics

The tablet hardness and friability tests were conducted with a YD-1 Tablet Hardness Tester (Tianjin Xingxue Instruments, China) and CS-A Tablet Friability Tester (TIANJIN UNIVERSITY RADIO FACTORY, China), respectively. Ten tablets were randomly selected, and their hardness value was recorded as the average ± S.D. The friability test was conducted according to the ChP (Chinese Pharmacopoeia 2010 [23]). Briefly, 35 tablets (weighing more than 6.5 g) were carefully blown off the attached powder with an air blower, accurately weighed, and then put into the spherical container of the friabilator, and rotated at 25 rpm for 4 min. The tablets were then collected, the residual power blown off, and carefully reweighed. The percent of friability was calculated. The result was obtained from the average of three determinations. A $\%_{Friability}$ less than 1 was qualified as acceptable.

The CU test was conducted under the recommendations and directions of the ChP. Briefly, 10 tablets were randomly selected and weighed, and the drug concentration was tested using HPLC (Waters 1525 binary bump, 2489 UV/Visible Detector, 2707 auto sampler, Model 1500 Column Heater, Breeze® 2 Software. The column was a Luna 5 μm C18(2), with dimensions of 150 mm × 4.6 mm (Phenomenex, Guangzhou FLM Scientific Instrument Co., Ltd). The mobile phase was methanol:ultrapure water:triethylamine = 80:19.5:0.5 (pH adjusted to 10.22). The drug strength of each tablet was recorded. The claimed drug strength (3 mg) was set as 100, and the average content A and standard derivation S were calculated. The Cu value was calculated as follows:

$$Cu = |A - 100| + 1.8 \times S \quad (1)$$

A Cu value smaller than 15 was qualified as acceptable. If the value was larger than 15, another 20 tablets were randomly selected, and the drug strength was tested. The total of the 30 tablets with average content A and standard derivation S was calculated, and the Cu value was calculated as

$$Cu = |A - 100| + 1.45 \times S \quad (2)$$

The Cu relative standard deviation (Cu $\%_{RSD}$) was also calculated.

Tablet *in vitro* dissolution testing was conducted according to the relevant ChP chapter. Briefly, the tablets were randomly selected and tossed into the unit, with the release medium being deionised water. The paddle method was used with a paddle speed of 50 rpm and 37 °C water circulation. At a certain time interval, 5 ml of release medium was drawn from each unit, and 5 ml of pre-heated release medium was immediately added to maintain the total volume at 500 ml. The drawn samples were filtered with a 0.45-μm filter, and the filtrate was collected then tested using HPLC. The cumulative release percent was calculated.

All data were processed with SPSS 19.0 (Independent-Sample T Test and One-Way ANOVA) and Origin Pro 9.0 if not otherwise specified.

3. Theory

The most important factor for achieving satisfied CU results for a low-dose oral formulation lies in the even distribution of API among all excipients during throughout the manufacturing process, i.e., mixing, blending and transferring steps. Therefore, the outcome mixtures of API and excipients need to present not only a small particle distribution span (minimising the segregation and agglomeration) but also good flowability (easily re-dispersing after storing) as well as good compactability to achieve tablets with small weight variation. In addition, with respect to the later processing steps, such as film coating, a smooth surface and a certain hardness are required for the product tablets.

4. Results

4.1. The evaluation of the granule/powder mixture

4.1.1. Repose angle and flowability of granule/powder mixture

The nozzle outlet diameters were 6 mm, 8 mm and 10 mm for the repose angle test and 10 mm, 15 mm and 20 mm for the flowability test. The paddle speed and appropriate diameter nozzles were chosen based on if the granule/powder mixture flow state was acceptable and had good reproducibility. The results were calculated as the average of three determinations. The results and lactose characteristics are presented in Tables 3, 4 and 5.

4.1.2. Particle size distribution

The granule/powder mixture was tested for particle size distribution using a dry powder dispersing system at a sample volume of 15 ml. The results are presented with comparisons of different types of lactose and same granulation method in Fig. 2. The mean and median diameter results are shown in Table 6. The particle size distribution results presented in Fig. 2 show the percentages of particles at certain diameters in total volume, illustrating the results of Table 6. The curves present the size distribution homogeneity results that could be numerically valued with SPAN.

Span, as a measure of the width of the size distribution, was calculated using the following equation:

$$Span = (d90 - d10)/d50 \quad (3)$$

Where d10, d50 and d90 in this equation were the equivalent volume diameters at 10%, 50% and 90% cumulative volume distributions, respectively.

4.1.3. DSC

Using DSC, the crystallisation, modification, polymorph transformation, melting, evaporation and decomposition processes can be studied. All of the lactose types and HPMCs were tested to determine their calorimetric information by DSC. The results are presented in Fig. 3. Performing DSC on a powder provides an insight into the structure of the powder particles. Glass transition and crystallisation peaks on the DSC curves indicated the presence of an amorphous structure in the particle, and an amorphous lactose structure can readily absorb water, which can give rise to caking problems [24]. These problems are, in turn, reflected by poor flowability and a steeper angle of repose. The melting point of PD6 is 225.40–226.60 °C. The DSC thermogram of commercial lactose displayed two distinctive endothermic peaks at approximately 150 °C–160 °C and 220 °C, which correspond to the dehydration of crystalline hydrate water and the melting of anhydrous α-lactose, respectively. The small exothermic peak approximately 160 °C (Fig. 3A–E)

Table 3
Repose angle, density and flowability of granules/powder mixture.

Granules/powder	Repose angle (°)	Evaluation based on repose angle	Density (g/ml)	Flowability (100 g/s)
D 110M WG	33.6	Good	0.421	12.5
D 125M WG	37.5	Fair	0.218	13.7
D 200M WG	26.0	Excellent	0.331	17.4
D 11SD WG	35.9	Good	0.506	5.3[a**]
D 110M DG	33.3	Good	0.270	11.3
D 125M DG	35.8	Good	0.278	16.1
D 200M DG	41.3	Passable	0.312	16.3
D 11SD DG	42.0	Passable	0.517	10.2
D 21AN DG	32.2	Good	0.261	12.7
D 11SD DC	32.1	Good	0.490	5.7 [b**]
D 21AN DC	39.5	Fair	0.478	6.8 [b**]

[a] Data compared among batches that manufactured with same granulation method. ($^{*}p < 0.05$, $^{**}p < 0.01$).
[b] Data compared between direct compression method and dry granulation method. ($^{*}p < 0.05$, $^{**}p < 0.01$).

Table 4
Bulk density, tapped density, Carr index and Hausner ratio of the lactose.

Lactose	Bulk density[a] (g/ml)	Tapped density[a] (g/ml)	Carr index[a]	Hausner ratio	Evaluation based on Carr index and Hausner ratio
D 110M	0.72	0.88	18.00	1.22	Fair
D 125M	0.68	0.85	20.00	1.25	Fair
D 200M	0.57	0.84	32.00	1.47	Very poor
D 11SD	0.60	0.71	16.00	1.18	Good
D 21AN	0.71	0.88	19.00	1.24	Fair
HPMC	0.332	0.445	27.08	1.37	Fair

[a] Data was from the document sent along with the lactose sample or official pamphlet.

Table 5
Bulk density, tapped density, Carr index and Hausner ratio the granules.

Granules/powder	Bulk density (g/ml)	Tapped density (g/ml)	Carr index	Hausner ratio	Evaluation based on Carr index and Hausner ratio
D 110M WG	0.545	0.617	11.84	1.13	Good
D 125M WG	0.486	0.590	17.74	1.22	Fair
D 200M WG	0.556	0.598	7.14[a*]	1.08	Excellent
D 11SD WG	0.360	0.450	20.00	1.25	Fair
D 110M DG	0.621	0.762	18.75	1.23	Fair
D 125M DG	0.643	0.736	12.90	1.15	Good
D 200M DG	0.589	0.706	16.67	1.20	Fair
D 11SD DG	0.606	0.732	17.44	1.21	Fair
D 21AN DG	0.719	0.785	8.33[a**]	1.09	Excellent
D 11SD DC	0.574	0.634	10.45	1.10	Excellent
D 21AN DC	0.562	0.656	9.09	1.10	Excellent

[a]Data compared among batches that were manufactured with same granulation method. ($^{*}p < 0.05$, $^{**}p < 0.01$).

Table 6
Particle size distribution of granules.

Batch	Mean	Median	d10	d50	d90	Span (d90–d10)/d50
D 110M WG	300.5	226.8	99.08	226.8	627	2.328
D 125M WG	340.5	281.4	82.32	281.4	689.2	2.157
D 200M WG	469.8	446.7	98.73	446.7	899.2	1.792
D 11SD WG	471.4	504.3	67.89	504.3	777.6	1.407
D 110M DG	101.7	86.60	8.664	86.6	218.5	2.423
D 125M DG	68.47	56.60	5.842	56.6	153.7	2.612
D 200M DG	57.35	43.09	4.009	43.09	138.7	3.126
D 11SD DG	118.5	88.49	15.68	88.49	237.3	2.504
D 21AN DG	183.8	144.3	9.853	144.3	425.1	2.878
D 11SD DC	142.4	128.7	22.30	128.7	277.4	1.982
D 21AN DC	194.4	189.4	34.56	189.4	363	1.734

corresponds to the crystallisation of amorphous lactose to primarily α-lactose, as previously reported [25].

4.1.4. SEM

The SEM was taken with magnifications of 100× and 400× for PD6 and 33×/40× and 100× for the other powder mixtures.

4.2. Evaluation of tablets

4.2.1. Hardness and friability

The hardness and friability test results are shown in Table 7. A $\%_{Friability}$ less than 1 was considered qualified as acceptable. All tablet batches were qualified under this criterion. For hardness results, although there is no quantified standard, it is generally considered that increased hardness is better for the following manufacture processes (coating, transferring and packaging). All of the DGT batches were harder and less friable than the corresponding WGT batches made with the same type of lactose.

4.2.2. CU and tablet weight

All of the batches of tablets were tested for CU, and the tablet weight was recorded. The results are presented in Table 8.

The further application of spray-dried lactose monohydrate with the wet granulation method was used for an even lower dosage strength of PD6 (Table 9). The CU was studied at different batch sizes, including 100 g (approximately 500 tablets), 500 g (approximately 2500 tablets) and 1 kg (approximately 5000 tablets). The hardness and friability results of all of the batches were qualified, and an *in vitro* dissolution test was run with good repeatability among different batch sizes (data not shown).

It was believed that because of the excellent flowability, spray-dried lactose could help excipients mix with the API more evenly than other types of lactose. To prove this hypothesis, another 4 types of commercial lactose, including Granulac® 200 (a lactose monohydrate), FlowLac® 100 (a spray-dried lactose monohydrate of Meggle), NF Lactose Monohydrate 314WG and NF Lactose Hydrate

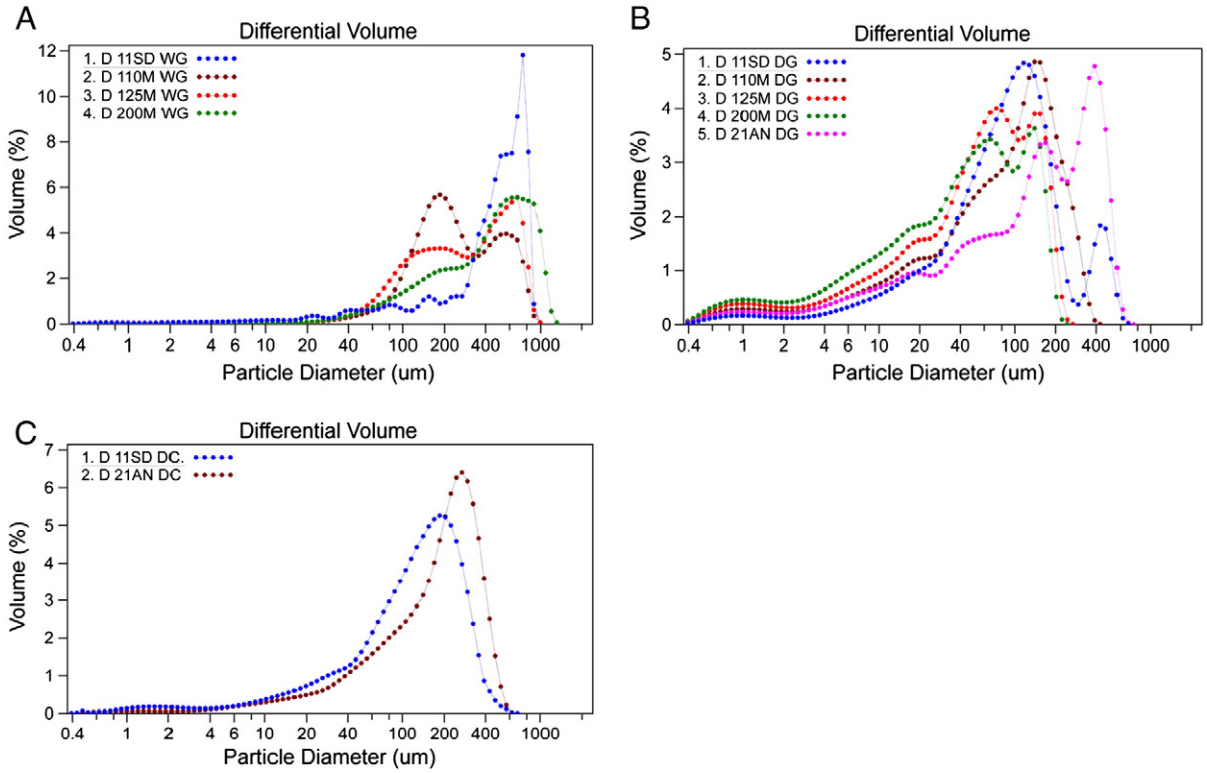

Fig. 2. Particle distribution of (A) granules obtained by wet granulation; (B) granules obtained by dry granulation and (C) powder mixture of correspondence lactose, HPMC K100LV CR and PD6 for direct compression.

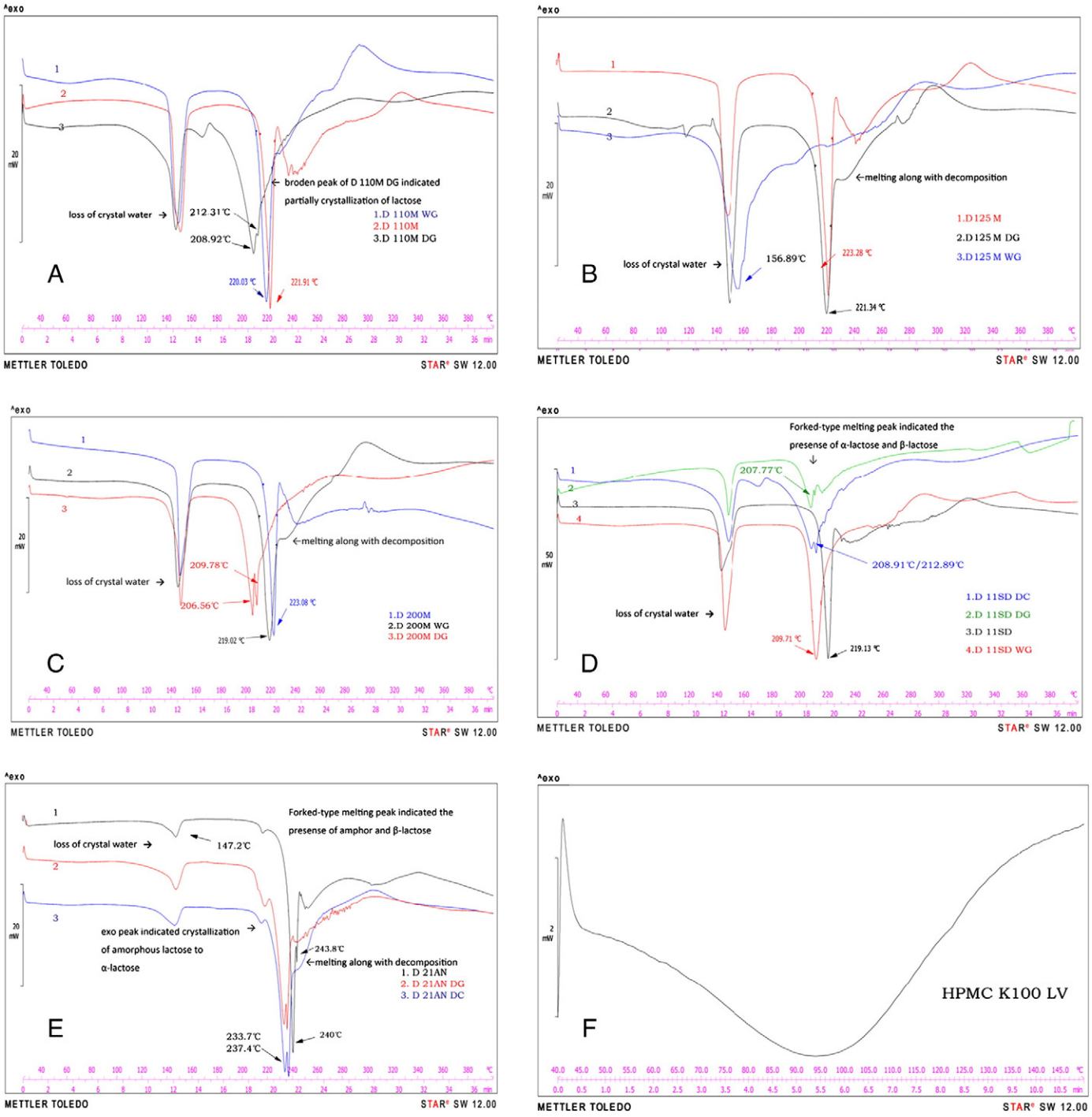

Fig. 3. DSC curves of WG, DG, DC and lactose, HPMC.(A) lactose, DG and WG of D 110M; (B) lactose, DG and WG of D 125M; (C) lactose, DG and WG of D 200M; (D) lactose, DC, DG and WG of D 11SD; (E) lactose, DC,DG of D 21AN and (F) HPMC k100 LVCR.

Monohydrate Spray Dry Fast Flo 316 t (Foremost) were used in the same formulation using the wet granulation tableting method. The CU results are listed in Table 10.

4.2.3. In vitro dissolution results — cumulative release profile

For the *in vitro* dissolution testing, the sampling time interval was set to 5 min, 20 min, 40 min, 1 h, 1.5 h, 2 h, and 3 h. The tablet dissolution process was photographed at 5 min and 40 min. The dissolution test was stopped after the cumulative release percentage became higher than 80% at successive time points. The drug concentration in the release medium at each time point was tested using HPLC, and the cumulative release curve was drawn with Origin Pro 9.0. PD6 has good solubility in water (Table 1) and tends to degrade into paliperidone in pH 2 HCl after 2 h. Therefore, deionised water was chosen as the preferred release medium. The release profile of D 11SD WGT in different release media was also studied.

The transport phenomena involved in the drug release from HPMC matrices are very complex because the micro- and macrostructures of HPMC exposed to water is strongly time-dependent. Numerous studies and a large variety of empirical and semi-empirical mathematical models have been reported in the literature with respect to determining the transport mechanisms and attempting to quantitatively predict the resulting drug release kinetics [26,27]. For the controlled-release formulation, four models (zero order, first order, Higuchi equation,

Table 7
Hardness and friability of tablets.

WGT	Hardness (kg/cm^2)	Friability (%)	DGT	Hardness (kg/cm^2)	Friability (%)	DCT	Hardness (kg/cm^2)	Friability (%)
D 110M WGT	4.47 ± 0.37	0.54%	D 110M DGT	9.18 ± 0.42	0.31%	D 11SD DCT	7.18 ± 0.43	0.27%
D 125M WGT	2.42 ± 0.58	0.65%	D 125M DGT	5.07 ± 0.51	0.22%	D 21AN DCT	5.28 ± 0.32	0.19%
D 200M WGT	4.93 ± 0.52	0.46%	D 200M DGT	9.40 ± 0.41	0.43%			
D 11SD WGT	8.69 ± 0.31	0.28%	D 11SD DGT	10.13 ± 0.34	0.25%			
			D 21AN DGT	4.14 ± 0.29	0.23%			

Korsmeyer–Peppas equation) were selected to describe the drug release kinetics. For the zero-order model, drug dissolution occurs from dosage forms that do not disaggregate, and the drug releases slowly. The equation is as follows:

$$Q_t = Q_0 + K_0 t \tag{4}$$

where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution and set as $Q_0 = 0$. K_0 is the zero-order release constant expressed in units of concentration/time. To study the release kinetics, the data obtained from *in vitro* drug release studies were plotted as the cumulative amount of drug released versus time. The zero-order model typically is used to describe the drug dissolution of matrix tablets with low-solubility drugs [28]. The first-order model has been used to describe the absorption and/or elimination of certain drugs. The release of the drugs and the first order kinetics can be expressed by the following equation:

$$Log\,C = Log\,C_0 – Kt/2.303 \tag{5}$$

where C_0 is the initial concentration of the drug, K is the first-order rate constant, and t is the time [29]. The data obtained are plotted as log cumulative percentage of drug remaining vs. time, yielding a straight line with a slope of −K/2.303. The first-order model typically is used as a description of water-soluble drug release from porous matrices. In 1961, Higuchi [30] published what is most likely the most famous and frequently used mathematical equation to describe the release rate of drugs from matrix systems. For oral matrix-system contained HPMC, the equation generally is presented in the following form:

$$M_t/M_\infty = Kt^{1/2} \tag{6}$$

where M_∞ is the absolute cumulative amount of drug released at infinite time, and K is a constant reflecting the design variable of the system [31]. The Higuchi equation can describe several types of modified release pharmaceutical dosage forms, such as the matrix tablets with water-soluble drugs. A modified Higuchi equation, the Korsmeyer–Peppas model [32], can describe drug release from a polymeric system, and the equation is generally in the following form:

$$M_t/M_\infty = Kt^n \tag{7}$$

M_t/M_∞ indicates the fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterise the different releases of cylindrical-shaped matrices. To fit this model, 60% drug release data were used. All of the batches of tablets from the *in vitro* dissolution test results were plotted and fitted with these four kinetic models, and the results are shown in Table 11.

First-order kinetic modelling was conducted only when neither the zero-order mechanism nor the Higuchi equation could describe the release profile of the tablets (defined as a correlation coefficient of $R^2 > 0.950$ for the curve fitting the kinetic model). Constrained by the limitation of data selection, the modelling could not be applied for the overall release profiles. The patterns were separated into several phases, and each phase was applied to the different kinetic models. For instance, for D 11SD DGT, the drug release profile pattern was satisfactorily modelled with the Higuchi equation ($R^2 = 0.995$) within 40 min. However, after this point, the release pattern changed and was fitted with zero-order model with an $R^2 = 0.952$. Alternatively, D 125M WGT was fitted with a zero-order model throughout the whole release pattern, which was better than all the other tablet batches. Because a zero-order model typically describes low solubility drugs from matrices wherein the dosage does not disaggregate (i.e., low mechanical strength within tablets), this finding may be the result of the low hardness of D 125M WGT (2.42 kg/cm^2, Table 7).

Table 8
Tablet content uniformity and tablet weight variation.

Tablet	Drug concentration[a]	Cu	Cu[b]	Cu[a]	Weight variation[e]
	(mg/per tablet)	$\lvert A^{10} - 100\rvert + 1.8 \times S^{10}$	$\lvert A^{30} - 100\rvert + 1.45 \times S^{30}$	RSD (%)	RSD (%)
D 110M WGT	3.08	14.61		1.27	3.90
D 125M WGT	3.19	13.85		3.90	2.87
D 200M WGT	3.67/3.39	36.39	21.73	4.04/4.34	3.41
D 11SD WGT	3.15	12.22[c]**		4.85	4.97
D 110M DGT	3.17	14.49		2.92	1.62
D 125M DGT	3.06	8.16[c]*		2.54	2.83
D 200M DGT	3.49/3.29	20.20	14.55	1.56/2.35	1.32
D 11SD DGT	3.18	12.60		3.14	1.12
D 21AN DGT	2.85	14.16		5.74	4.31
D 11SD DCT	3.10	6.39[d]**		1.89	0.96
D 21AN DCT	3.28/3.18	15.60	13.09	5.40/7.61	3.08

[a] The value before and after the slash indicated the drug concentration, Cu %RSD tested by HPLC with 10 tablets and 30 tablets respectively.
[b] $Cu\{\lvert A^{30} - 100\rvert + 1.45 \times S^{30}\}$ was calculated only when $Cu\{\lvert A^{10} - 100\rvert + 1.8 \times S^{10}\}$ was bigger than 15, superscript in the expression indicated the number of tablets used for test (batch size 100 g).
[c] Data compared between D 11SD WGT and D 200M WGT (*$p < 0.05$, **$p < 0.01$).
[d] Data compared between D 11SD DCT and D 21AN DCT. (*$p < 0.05$, **$p < 0.01$).
[e] $n = 20$.

Table 9
Tablet content uniformity of 3 mg, 1.5 mg and 0.75 mg dosage strength tablet at batch size of 100 g, 500 g and 1 kg[a].

Dosage strength and drug loading (w/w)	Batch size (kg)	Cu $\lvert A^{10} - 100\rvert + 1.8 \times S^{10}$	
3 mg (1.5%)	0.1	12.22	13.51
	0.5	12.57	
1.5 mg (0.75%)	1	1.70	7.29
	0.1	12.79	
	0.5	11.23	1.49
	1	8.90	9.46
0.75 mg (0.375%)	0.1	14.37	
	0.5	8.98	8.67
	1	13.11	14.74

[a] Lactose and method was D 11SD and wet granulation respectively.

5. Discussion

5.1. Granule/powder mixture properties

5.1.1. Flowability and particle size distribution

The flowability of granule/powder mixtures is extremely important for the pharmaceutical industry, especially for those aspects involving solid excipients [33]. The Carr index [34] and Hausner ratio [35] are both empirical definition used with a powder or granular material that are used to describe the material as free-flowing or possessing a cohesive tendency (to cake). The former is generally uses as an indication of the compressibility characteristics, whereas the latter represents flowability. Another evaluation factor is the angle of repose, which is the steepest angle of descent of the slope relative to the horizontal plane when the material on the slope face is on the verge of sliding. The angle is in the range 0°–90° and is related to the density, surface area and shapes of the materials. A pile of materials tends to be more free-flowing when forming a flatter angle (i.e., when it has lower repose angle). Because the results vary depending on the methods used and evaluation basis [21], and different evaluation indexes are used to describe the flowability of a certain material, no single test can thoroughly quantify flowability. Therefore, the results obtained are the combinations of the material physical properties and the equipment/method used for processing, both of which could affect the flow of materials. In this study, several frequently used indexes were selected to evaluate the flow properties of all granules/powders, and the classical methods were used for testing. A suitable paddle speed and outlet nozzle diameter were chosen based on studies of material–silo interactions (e.g., the particle-to-wall friction coefficient) [11] and shear force on the flow function variation [12] of materials.

Generally, D 11SD was "Good" in flow ability and superior to any other type of lactose, whereas D 200M, the milled lactose monohydrate with a diameter of most proportions smaller than 100 μm, was "Very poor." With respect to D 110Mand D 125M, the proportion of particles smaller than 63 μm were less than 20% and 40–70%, respectively, and thus were more free-flowing when compared with D 200M (63 μm %, passing rate 50–65%). At the same time D 110M was better than D 125M, as expected. For the anhydrous lactose D 21AN and spray-dried lactose monohydrate D 11SD, the former contained a greater proportion of particles larger than 250 μm in diameter (%passing rate ≥98 and ≥80, respectively). Thus, these types of lactose tended to be stable inside or on the border of the sloping face under the same gravity action because of the friction coefficient. This result was confirmed with the large repose angle of D 21AN DC (39.5° Table 3), indicating a "Fair" flow property; however, when evaluated based on the Carr's index/Hausner ratio, the result was "Excellent."

After mixing lactose with HPMC K100 LVCR and PD6, the flow property changed. The granulation process altered the mixtures properties significantly, as expected. Compared with dry granulation, the wet granulation method improved the flowability of D 200M significantly (from "very poor" to "excellent"). SEM (Fig. 4E and Fig. 5D) revealed the morphological changes from a fine lactose mixture into much larger irregular cube-shaped agglomerate granules. It was hypothesised that during the wet granulation process, smaller-sized lactose particles, i.e., larger specific surface area, would more easily adhere onto the HPMC matrices and, thus, larger granules would tend to form. This result was confirmed by the span values of D 110M WG and D 125M WG (2.328, 2.15, respectively). SEM revealed a large proportion of free lactose that did not combine to form agglomerated granules. In addition, during the dry granulation tableting method, HPMC, PD6 and lactose formed granules through compression and slugging by physical mechanical force, and the size distribution was similar to the corresponding lactose particles; however, the morphological properties were altered, which could be observed on SEM results. The edges and corners formerly observed on lactose primarily disappeared (Fig. 4C, D, E and Fig. 5E, F, G), and the surface became rougher and attached to a stick-shaped HPMC.

For the WG products, particles with the sizes approximately 150–200 μm and 600–700 μm made up the largest portion (4%–6%), especially D 11SD WG, for which approximately 11% particles were 700 μm. The good uniformity of the size distribution (the smallest size span of all WG and DG) and the relatively larger particle sizes benefited the flowability, as predicted [36]. For DG, approximately 5% of the granules were 50 μm (D 125M and D 200M), 100 μm (D 11SD and D 110M) and 400 μm (D 21AN). Compared with the WG products, the DG products were more "inhomogeneous." The granule sizes were not constrained by the mesh of sieves, but their brittle nature tended to drive loose-attached particles/powder to easily fall off the granules during processing (Fig. 5E–I). This occurred due to adhesive Van der Waals interactions for the fine-grained dry-bulk solids (dry granules). In contrast, for moist bulk solids (wet granules) liquid bridges primary role, making these particles more durable [37]. Contrasted with D 200M WG, which had the largest particle size, D 200M DG had the smallest granules. Although the size differences among D 110M DG, D 125M DG and D 200M DG are subtle (Table 6), the highest span value being associated with D 200M DG (3.126) indicated that the uneven distribution would be more significant than granules with other forms of lactose. The precipitating of larger granules down to the bottom of the whole pile of powder would occur during storage, transportation or after over-mixing, although the acceptable flowability of D 200M DG could allow for easy and even re-distribution during the manufacturing process. This paradox eventually affected the CU outcome.

For D 11SD, the spherical shape provided excellent flowability after mixing with HPMC and PD6. However, after wet/dry granulation, the flowability was degraded to "Fair." The spherical properties

Table 10
Content uniformity results of the tablets using lactose of Meggle and Foremost.

WGT lactose	Drug concentration (mg/per tablet)	Cu $\lvert A^{10} - 100\rvert + 1.8 \times S^{10}$	Cu[b] $\lvert A^{30} - 100\rvert + 1.45 \times S^{30}$	Cu[a] RSD (%)
Granulac® 200	3.24/3.21	26.70	19.64	3.72/3.11
FlowLac® 100	3.20	12.68		3.47
314WG	3.57/3.32	24.07	15.67	0.95/1.18
Fast Flo 316	3.21	13.55		2.09

Table 11
Kinetic modeling of drug release.

Batch	Zero order		First order	Higuchi equation		Korsmeyer–Peppas	Drug diffusional release mechanism	
	R^2	K_0 (h^{-1})	R^2	R^2	kH ($h^{-1/2}$)	R^2	Release exponent (n)	Based on release exponent (n)
D 110M WGT	0.958	123.6		0.963	127.6	0.998	0.635	Anomalous (non-Fickian) diffusion
D 125M WGT	0.982	29.62		0.958	65.28	0.991	0.521	Anomalous (non-Fickian) diffusion
D 200M WGT	0.941	15.75		0.987	43.15	0.958	0.472	Anomalous (non-Fickian) diffusion
D 11SD WGT	0.935	61.10		0.994	78.85	0.999	0.383	Quasi-Fickian diffusion
D 110M DGT	0.919	62.56		0.968	95.75	0.999	0.505	Anomalous (non-Fickian) diffusion
D 125M DGT	0.915	64.08		0.983	84.91	0.999	0.445	Quasi-Fickian diffusion
D 200M DGT	0.965	36.96		0.991	67.34	0.991	0.389	Quasi-Fickian diffusion
D 11SD DGT[a]	0.945	49.96	Within 40 min 0.995	0.896	67.3	0.999	0.300	Quasi-Fickian diffusion
D 21AN DGT	0.846	39.77		0.952	71.35	0.952	0.570	Anomalous (non-Fickian) diffusion
D 11SD DCT	0.928	55.46		0.988	9.99	0.999	0.356	Quasi-Fickian diffusion
D 21AN DCT	0.811	49.69	0.989	0.808	82.86	0.897	0.328	Quasi-Fickian diffusion

[a] D 11SD DGT, witin 40 min, fitted Higuchi equation with $R^2 = 0.995$, after 40 min, fitted zero order with $R^2 = 0.952$.

were nearly lost for D 11SD DG, and the granules presented an irregular shape and differed in size significantly. Nearly no intact spray-dried lactose monohydrate particle could be seen in SEM photos of D 11SD DG. However, D 11SD WG still presented uncombined intact spherical lactose (Fig. 5D and H), meaning the flowability would, to a certain extent, remain at a good level. The repose angle results (35.9° "Good" for D 11SD WG and 42° "Passable" for D 11SD DG) confirmed this.

For anhydrous lactose D 21AN, mixing with HPMC K100 LV CR improved the flowability significantly ("Fair" to "Excellent"), and dry granulation did not make a great deal of difference in ameliorating the flowability (from "Excellent" to "Excellent"). The brittle nature of anhydrous lactose allowed for re-compaction without loss of tabletability. This result explains why the Carr's index (the index of compressibility) remained nearly the same for D 21AN DC and D 21AN DG (9.09 and 8.33, respectively).

5.1.2. DSC curves

DSC results can semi-quantitatively assess the material/mixture purity and be used for analysing the compatibility of the drug and excipients [38]. In this low-dose formulation, lactose composed most of the whole materials. Hence, the DSC curves presented the reaction of lactose with the drug and HPMC based on the disappearance, shifts or other changes of the endothermic peaks. Because all forms of lactose are composed of some proportion of α-lactose and β-lactose, the processing steps would differentiate these two identical peaks. Note that after dry granulation, the fork-type peak would clearly be observed on DSC curves [39] (Fig. 3). This effect may be explained by how the dry granulation process affected the crystal form and made the lactose change from amorphous into an α-form. In contrast with these results, the crystal form of lactose was stable after wet granulation. As the results indicated that the first endothermic peak (140 °C to − 160 °C, Fig. 3A–E) of lactose (indicated the loss of crystal water) was nearly unchanged, the shifts of temperature in the second endothermic peak (indicating the degradation) of DGT (almost 10 K downward) suggest that a non-eutectic interaction occurred between the lactose and the drug. For WGT and D 21AN DCT, the platform adjoining the second endothermic peak (which remained nearly the same) indicated melting along with decomposition. As for D 125M WG, the second endothermic peak disappeared and merged into one endothermic peak, with a significantly broadening width (Fig. 3B). This latter effect could be explained by an interaction between D 125M, HPMC and PD6 during the wet granulation process, wherein the drug dissolved in the matrix when the mixtures melted during the heating process. It was hypothesised that the moderate diameter of the lactose particle, acceptable flowability along with an edged, prism-shaped form allowed for D 125M to evenly mix with HPMC, leading to better water absorption over the entire wetting mass and forming suitable HPMC matrices. The hardness of D 125M WGT was the lowest (2.42 ± 0.58 kg/cm^2), and the friability of the product was the highest (0.65%) (Table 7). These results may confirm the previous assumption. In addition, the *in vitro* dissolution profile of D 125M WG differed from all the other tablets by exhibiting a zero-order kinetic mechanism (Table 11, Fig. 6A). With respect to D 21AN, the anhydrous form of lactose had an endo peak area that was relatively smaller than the other types of lactose, and the amorphous state of lactose is very hygroscopic and readily absorbs water onto the powder surface. This water causes dissolution of the lactose and forms liquid bridges between particles {Teunou, 1999 #185}. This may explain the nearly immediate swelling of the tablet after contact with water and the persistence of the swelling state after 40 min as shown in Fig. 7 (B&D 11).

The DSC curves of D 110M DG (Fig. 3A), such as the concave on the left side of the melting peak, broaden because of the partial crystallisation of the mixture. This phenomenon also repeated with D 200M DG, D 125M DG, 11SD DC, 11SD DG, but not in D 11SD WG. The shift of the second endothermic peak in WG was clearly observed in D 11SD WG. The peak remained relatively sharp (no abrupt broadening) indicating good compatibility between the drug and excipients after the wet granulation process. That is, spray-dried lactose monohydrate may stabilise API and HPMC after wet granulation because of the resulting special spherical structure.

5.2. Tablet evaluation results

5.2.1. Hardness, friability, CU and tablet weight variation

Generally, all of the DGT tablets had double the hardness of the WGT tablets made with corresponding lactose. The tablets made with D 11SD were harder compared with those made with other forms of the lactose. All of the WGT tablets were more fragile than DGT tablets made with corresponding lactose.

For low-dose formulations, a weight variation was often accompanied by a change in the $Cu\%_{RSD}$ [40,41], of which less than 5% was considered qualified. Controlling tablet weight variation is one of the advantages of spray-dried lactose monohydrate. As expected, the smallest weight variation was presented by D 11SD DCT ($\%_{RSD} = 0.96$). The Cu value of D 11SD DCT was also the smallest. This may be explained by the excellent flowability and narrow size distribution of D 11SD DC, which could help PD6 distribute more evenly in the whole volume of powder mixture. Therefore, less segregation could occur during the whole manufacturing process [40]. This was consistent with D 21AN DGT, D 21AN DCT and D 200M WGT, which all exhibited "Excellent" flowability (Table 5 and Table 10). However, the latter two batches of tablets were not qualified in Cu results for the first 10 tablets tested. D 21AN DCT passed after 30 tablets were tested, but again D 200M WGT failed. These results might be explained by the larger granule size, smaller particle span and good compressibility of D 200M WG, as subtle changes in filling weight during compression can cause different drug loading outcomes in tablets. The

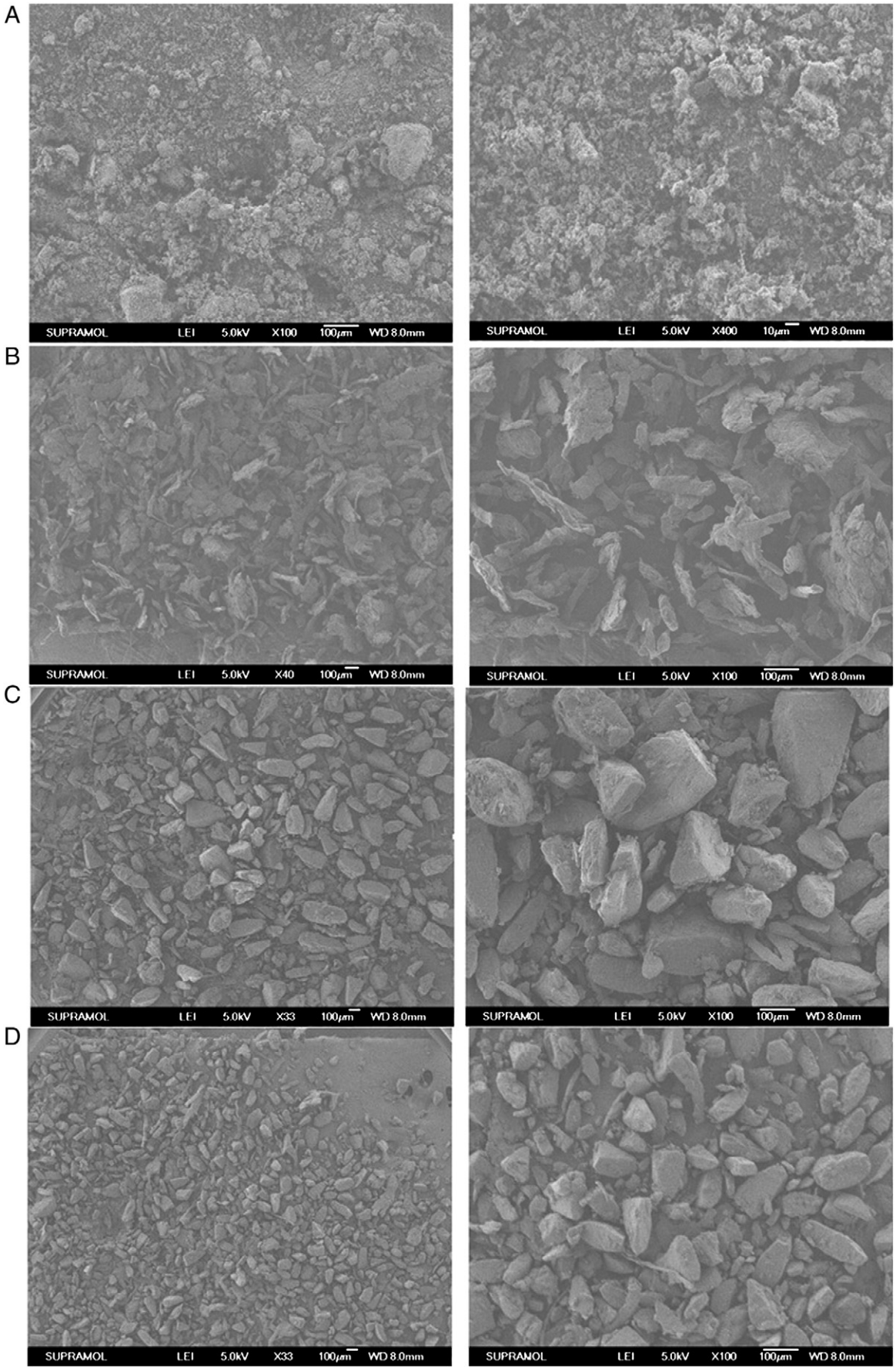

Fig. 4. SEM of powder mixture (A) PD6; (B) HPMC K100 LV; (C) D 110M DC; (D) D 125M DC; (E) D 200M DC; (F) D 11SD DC and (G) D 21AN DC.

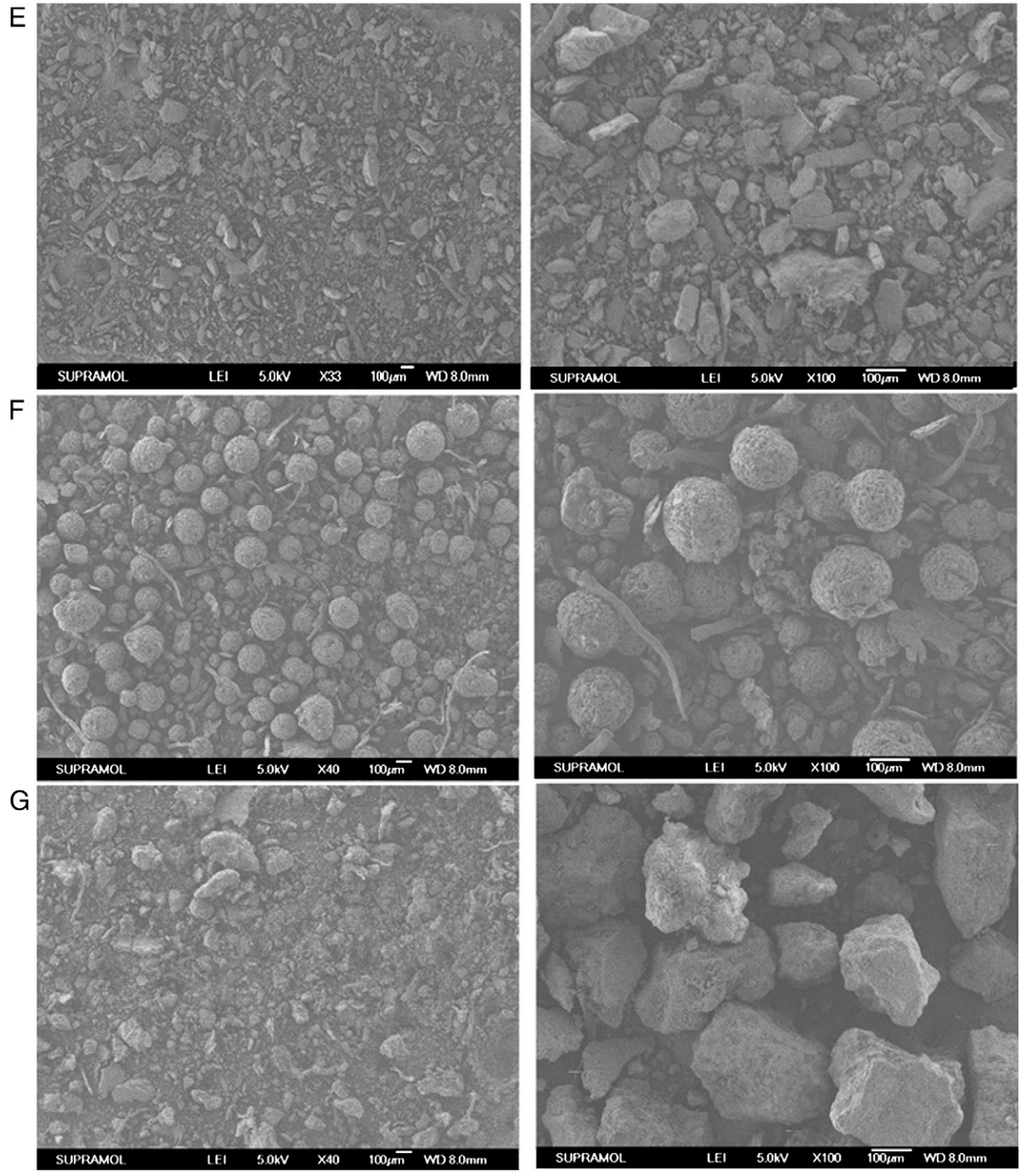

Fig. 4 (*continued*).

tablet evaluation results of D 11SD WGT confirmed this suggestion in one other aspect. Although D 200M WG and D 11SD WG presented similar particle size distributions, D 11SD WG was just "Fair" in compressibility and flowability, and the spherical lactose particles unattached to wet granules were able to freely fill in the mould during compression. Those particles were simply lactose that did not contain drug, and so the outcome drug loading would not deviate from the desired dosage strength.

For all of the DGT tablets, the Cu results were acceptable, but D 200M DGT again failed in the first Cu test with 10 tablets, and then qualified in the second round 30-tablet test. Because D 200M is milled lactose with high compactability, the lactose could mix with PD6 (also milled before being used) extremely finely, leading to a much higher drug loading than designed. The D 200M DGT tablets passed the second CU test due to the low weight variation ($\%_{RSD} = 1.32$) compared with that of D 200M WGT tablets. The particle size and tablet weight affected the outcome CU.

Overall, for this low-dose formulation, wet/dry granulation and direct compression were all suitable with sieved lactose D 110M, D 125M, the spray-dried lactose monohydrate D 11SD and the anhydrous lactose D 21AN.

5.2.2. In vitro dissolution test and kinetic modelling

Paliperidone derivatives displayed a much longer $T_{1/2}$ than paliperidone, and *in vivo* biodistribution results in rat indicate that PD6 is primarily absorbed in the stomach [1]. Therefore, a preparation with gradual but total drug release within 2 h was needed.

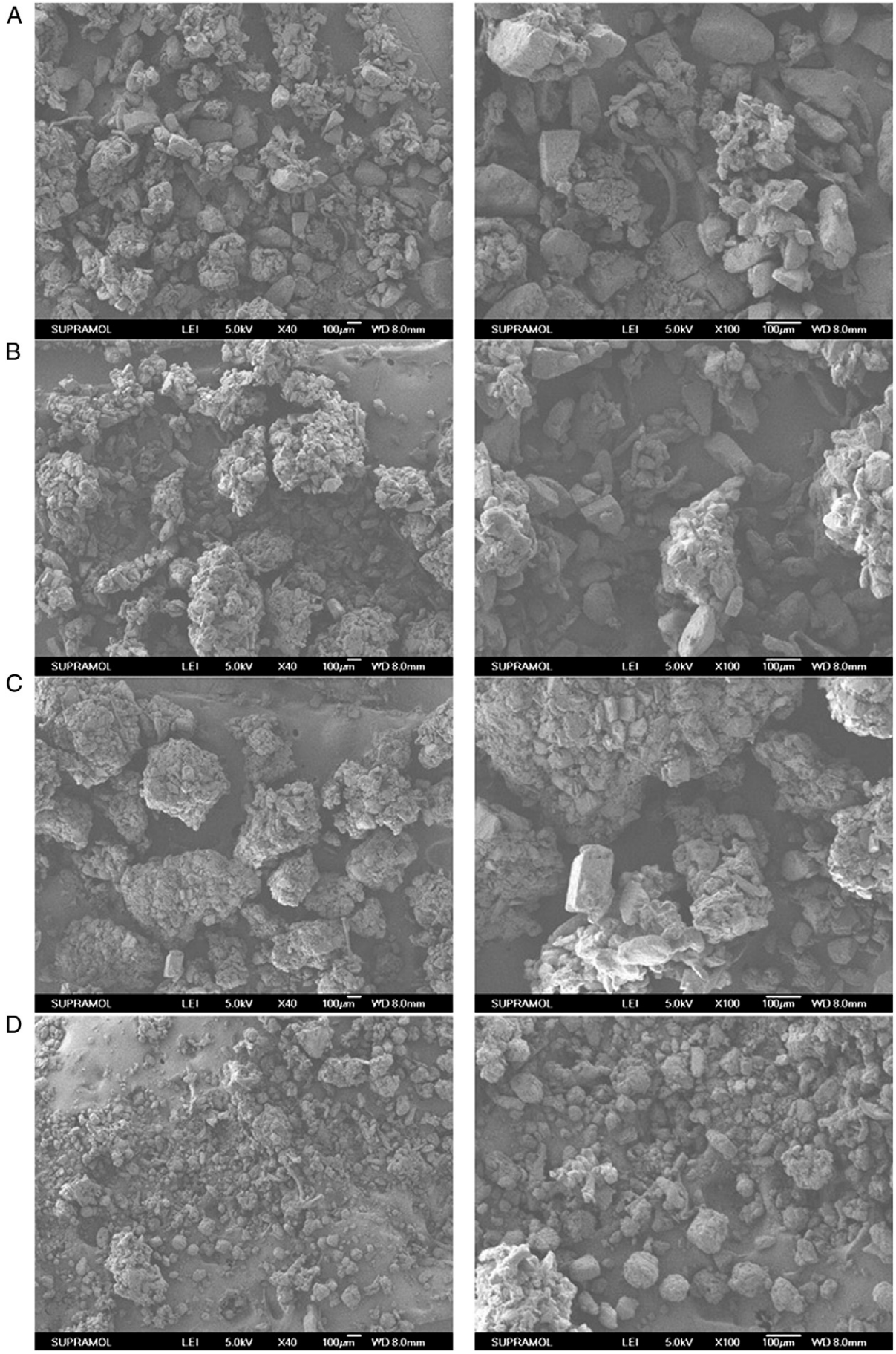

Fig. 5. SEM of (A) D 110M WG; (B) D 125M WG; (C) D 200M WG; (D) D 11SD WG; (E) D 110M DG; (F) D 125M DG; (G) D 200M DG; (H) D 11SD DG and (I) D 21AN DG.

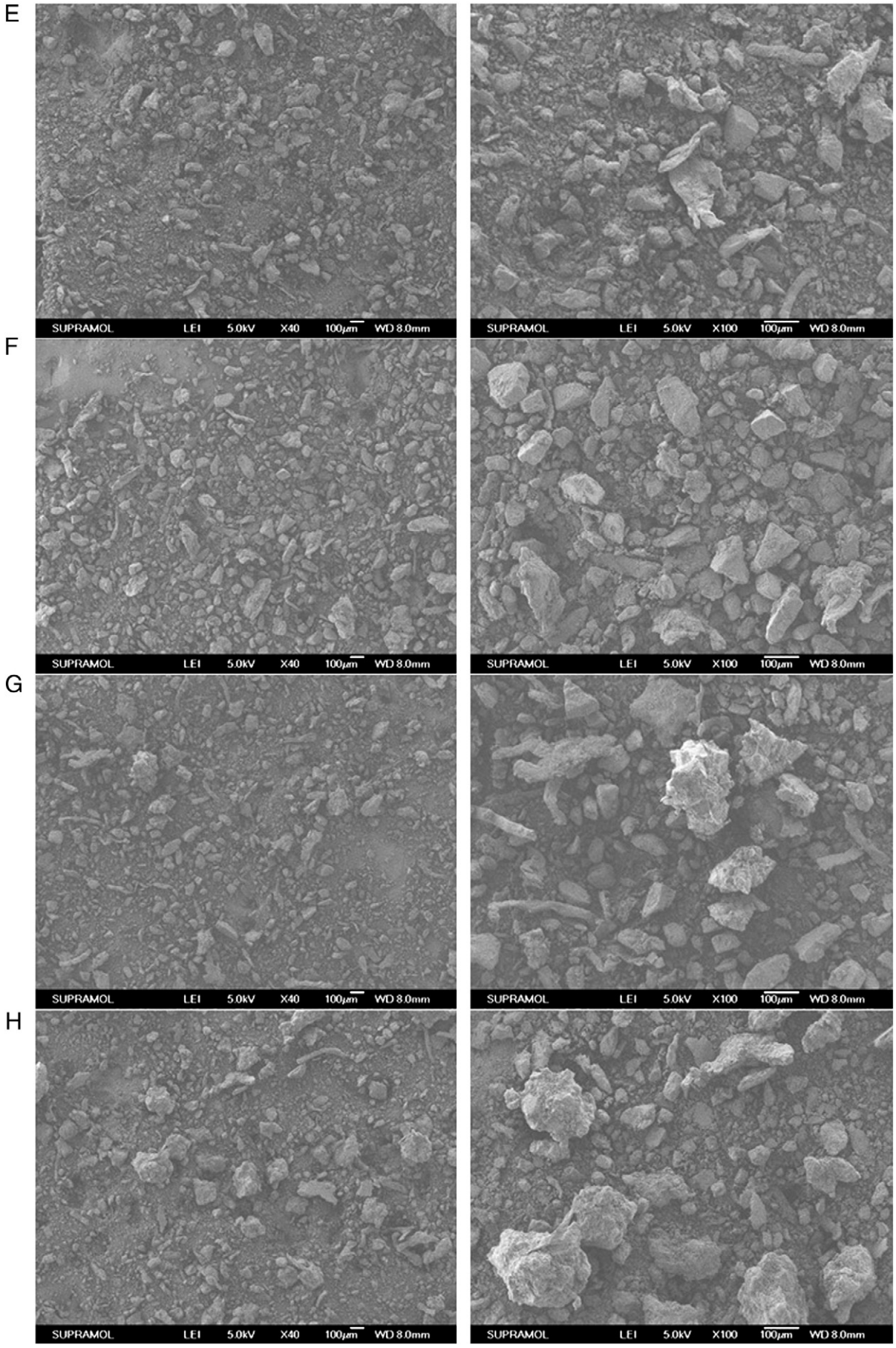

Fig. 5 (*continued*).

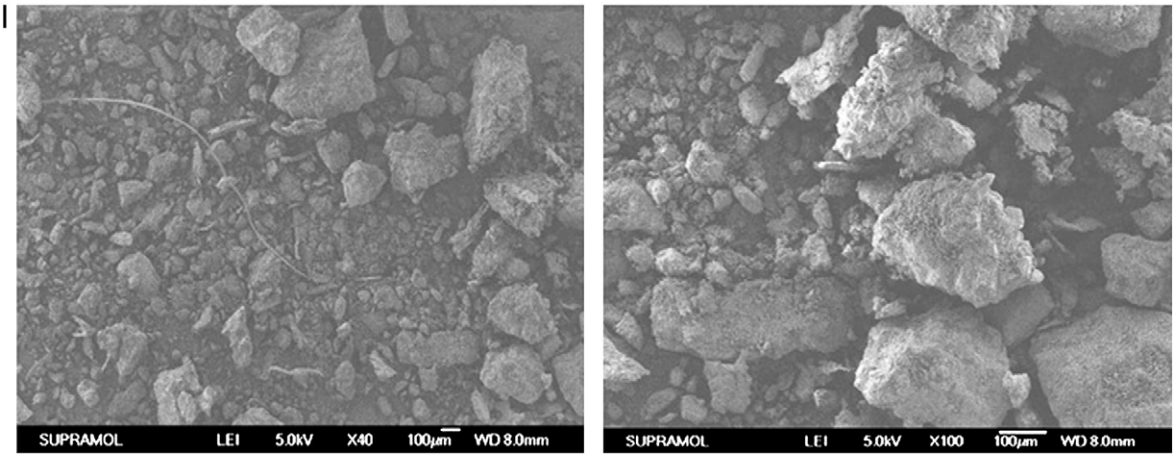

Fig. 5 (*continued*).

The release pattern of D 125M WGT was best fitted with zero-order release kinetics, but other WGT release profiles were better fitted with the Higuchi equation. The release rate of D 110M WGT was the fastest, followed by D 125M WGT. The slowest tablet was D 200M WGT. Based on the correlation coefficient values, WGT batches fit the Korsmeyer–Peppas equation quite well ($R^2 = 0.958–0.0999$). Batches that were made with sieved/milled lactose monohydrate all displayed anomalous (non-Fickian) diffusion release mechanisms, i.e., drug release was driven both by concentration gradient and polymer matrix relaxation. Considering the initial drug release amount at the first time point (5 min), D 110M WGT release was nearly double the other two WGT batches. As can be seen from the photos taken at 5 min (Fig. 7A 3), D 200M WGT swelled nearly immediately after entering the release medium but was still able to maintain a whole tablet shape at 40 min (Fig. 7B 3). D 110M DGT, in the contrast, presented an intact tablet shape at the beginning but gradually dissolved and diminished. The k_H ($t^{-1/2}$) values were inversely proportional to size distribution results of the corresponding granules.

D 11SD WGT tablets, unlike all the other WGT tablets, presented a quasi-Fickian diffusion (case I transport) release mechanism. The release exponent (n) value (0.383, $R^2 = 0.999$) indicated that diffusion was the dominant mechanism of drug release, with partial polymer chain relaxation. The release profiles of D 110M WGT and D 11SD WGT were similar at first analysis, but this was the result of complex factors (Fig. 7A, C 1 and 4).

A similar pattern was observed for DGT as well, i.e., DGT made with sieved/milled lactose monohydrate fit the Higuchi equation with high a linear relationship (R^2 0.968–0.991). However, for D 11SD DGT and D 21AN DGT, the release patterns periodically presented first-order release.

As for D 110M DGT, D 125M DGT, D 200M DGT, the correspondent granule particle sizes gradually decreased. In contrast with the prediction, D 110M DGT did not present the overall fastest release pattern. Instead, D 125M DGT initially released more than 30% of the drug at the first time point (5 min) (Fig. 6B) because the tablet nearly immediately dissolved and swelled after its contact with release medium (Fig. 7C 8). The release mechanism of D 110M DGT was anomalous (non-Fickian) diffusion, which differed from the other two DGT batches (quasi-Fickian diffusion). To a certain extent, HPMC was not functional as a polymer matrix for controlling the drug release from dry granulation tablets as it did in wet granulation tablets (significant at the $p \leq 0.05$ level for D 125M WGT/DGT and $p \leq 0.01$ level for D 200M WGT/DGT). However, for D 110M DGT and D 11SD DGT, the dry granulation tableting method slowed the overall release profile (significant at $p \leq 0.05$ levels) compared with the wet granulation method. This might be explained by the fully functioning HPMC, and the baseline shift that indicated the glass transition of polymer nearly disappeared on the DSC curves (Fig. 3A and D). This result might be explained by the thermo changes on the DSC curves (Fig. 5A and D). The peak shifts to lower temperature on the D 110M/D 110M DG curves (221.91 °C/208.92 °C, Fig. 3A) and the D 11SD/D 11SD DG curves (219.13 °C/207.77 °C, Fig. 3D), but the changes of temperature were smaller than those of D 125M/D 125M DG (223.08 °C/206.66 °C, Fig. 3B) and D 200M/D 200M DG (221.34 °C/156.89 °C, Fig. 3C). This could be explained by the near homogeneity of the wet granules in terms of particle distribution. The forked-type peak, which indicated the existence of α-lactose and β-lactose, were also relatively smaller as seen on the D110M and D 11SD DSC curves. The lactose forms in D 110M DG and D 11SD DG were much more stable and maintained their original properties. Therefore, D 11SD DGT fit the Higuchi equation with $R^2 = 0.995$ in the initial 40 min, and the release pattern changed then to a first-order pattern ($R^2 = 0.952$), unlike all the other DGT batches.

With respect to anhydrous lactose D 21AN, neither dry granulation nor the direct compression method significantly affected the thermodynamics. The diffusion release mechanisms were anomalous diffusion for D 21AN DGT and quasi-Fickian diffusion for D 21AN DCT. The difference could be seen clearly by visual observation (Fig. 7A&B 6, C&D 11). At the same time, those two batches both fit first-order kinetics, especially D 21AN DCT, which presented an overall first-order release pattern with $R^2 = 0.989$, which indicated D 21AN DCT could certainly be used as a sustained-release tablet.

5.3. Using spray-dried lactose monohydrate in wet granulation method

Compared with dry granulation and direct compression, wet granulation might be the most common method used in the pharmaceutical industry, being performed with various manufactured equipment from the laboratory scale to the pilot plant, as well as during scale-up and the actual production process [7,40]. Compared to the common wet granulation recommended sieved/milled lactose monohydrate, using spray-dried lactose monohydrate in wet granulation not only resulted in good properties, such as fast and good flow states (5.3 s for 100 g granules under gravity, Table 3) and the smallest size distribution span (1.407, Table 6), but also satisfied the outcome CU results from the laboratory scale (100 g and 500 g) to scale-up level (1 kg). The special properties of spray-dried lactose can reduce the degree of segregation/agglomeration of granules during throughout the manufacturing process. The product tablets presented a qualified release profile, good hardness and low friability. The latter two factors are very important for the following processing of tablets, such as coating, filling and storage.

This conclusion was confirmed using spray-dried lactose monohydrate FlowLac® 100 from Meggle and NF 316 Fastflo from Foremost (Table 10). Compared with fine-milled lactose monohydrate

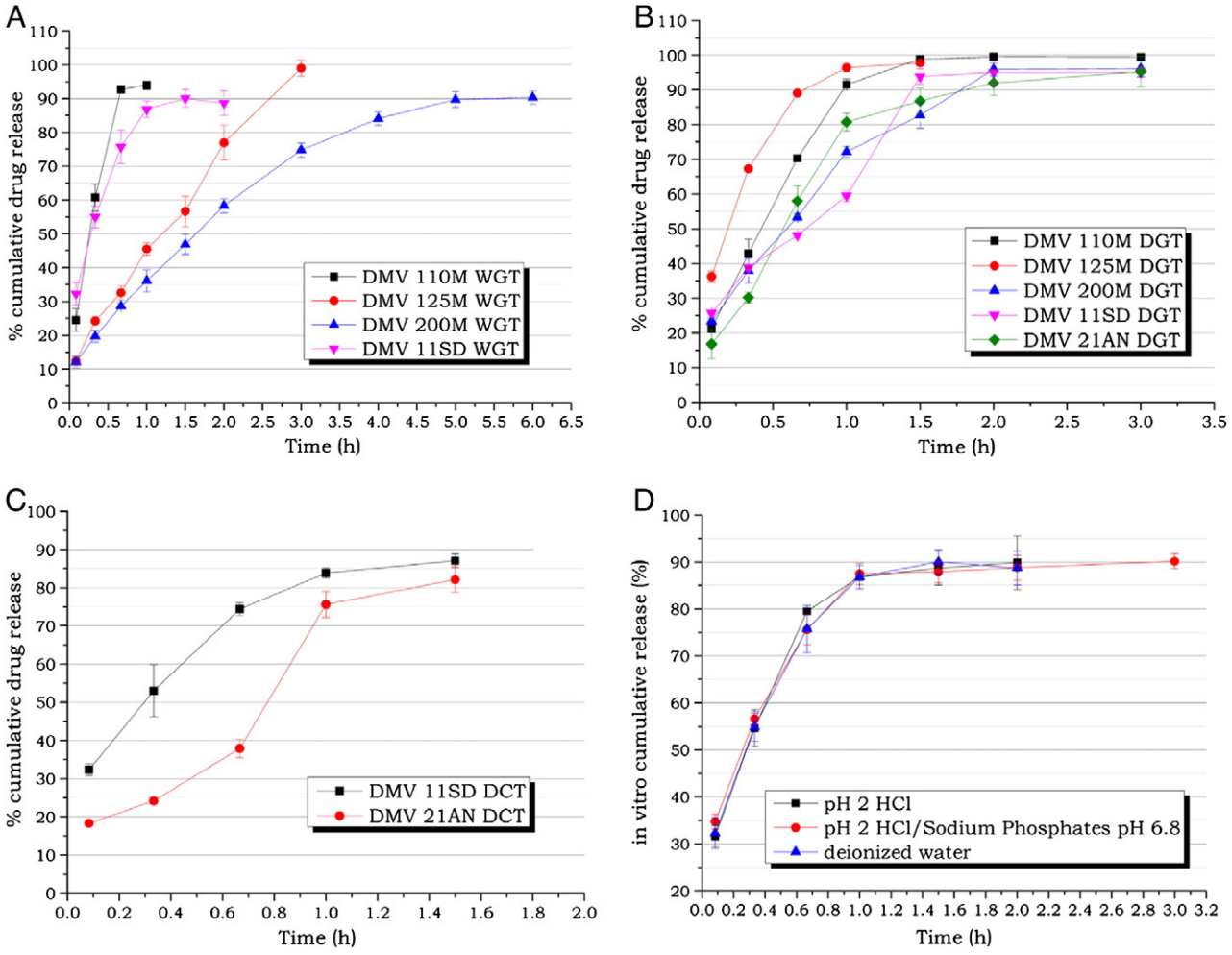

Fig. 6. *In vitro* cumulative release profile of tablets. (A) WGT;(B) DGT;(C) DCT and (D) D 11SD WGT dissolution with different release medium (deionized water, pH2 HCl, pH2 for first 2 h and adjusted pH to 6.8 with sodium phosphates) (n = 6).

GranuLac® 200 from Meggle and crystal lactose monohydrate NF 314_GENERAL from Foremost, the CU test was only qualified for the former two types of lactose. The uniformity of granules made with D 11SD by wet granulation displayed better compatibility with the drug and HPMC in drug-excipient compatibility testing (data not shown), which benefits all of the processing steps in scale-up, where the particle properties are extremely important[42]. D 11SD was selected as the most suitable form of lactose for further larger batch size experiments. The same formulation was repeated at a batch size of 500 g and 1 kg, and good CU results were obtained. The same manufacturing method was applied to a lower drug loading of 0.75% (1.5 mg/per tablet) and 0.375% (0.75 mg/per tablet) at batch sizes of 100 g, 500 g (up to 2500 tablet yield), and 1 kg (up to 5000 tablet yield) and repeated twice. These results are presented in Table 9. With the satisfied CU even at a low drug loading of 0.375% and good reproducibility in the pilot and scale-up process, this simple formulation using spray-dried lactose monohydrate in wet granulation has been proven to be suitable for application to other insoluble,

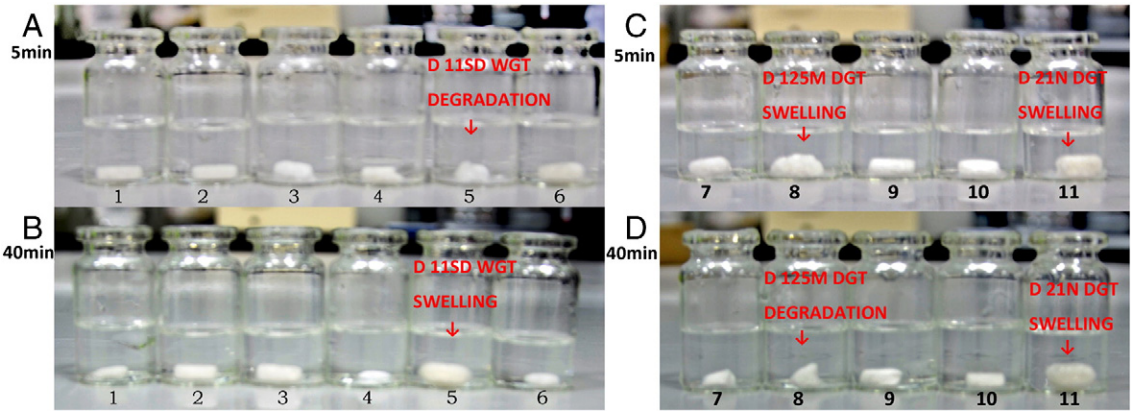

Fig. 7. Photos of tablets in dissolution test. 1. D 110M WGT, 2. D 125M WGT, 3. D 200M WGT, 4. D 11SD WGT, 5. D 11SD DCT, 6. D 21AN DCT, 7. D 110M DGT, 8. D 125M DGT, 9. D 200M DGT, 10. D 11SD DGT and 11. D 21AN DGT at (A) & (C) 5 min (B) & (D) 40 min.

long $T_{1/2}$ drugs. Various *in vitro* release profiles obtained using different types of lactose and methods could also be helpful in other formulation designs.

6. Conclusion

A simple, low-dose oral formulation using spray-dried lactose monohydrate in wet granulation was established. Different brands and types of lactose were selected, and different manufacturing methods (wet granulation, dry granulation and direct compression method) were adopted. Although lactose monohydrate is recommended for wet granulation and spray-dried lactose monohydrate is considered to be more suitable for direct compression, our study demonstrated, surprisingly, that using spray-dried lactose monohydrate in a wet granulation may produce more acceptable flowability of the granules and much better CU results with no need of adding other excipients, such as microcrystalline cellulose or CAB-O-SIL®. The product tablets presented significantly varying evaluation results, although the tablets prepared with different lactose types presented similar properties when prepared using the same type of lactose. Our study also suggests some potential explanations for predicting drug release profiles by particle size distribution, DSC and tablet hardness. These findings may aid in the further understanding of pharmaceutical particles in actual production phases, and this formulation design could be applied to other insoluble API low-dose formulations.

Abbreviations

PD6	Pentyloxyl paliperidone hydrochloride
WG	Granules obtained by wet granulation
DG	Granules obtained by dry granulation
DC	Powder mixture of corresponding lactose, HPMC and drug
WGT	Tablets obtained by wet granulation method
DGT	Tablets obtained by dry granulation method
DCT	Tablets obtained by direct compression method
D 110M	DMV Pharmatose® 110M sieved lactose monohydrate
D 125M	DMV Pharmatose® 125M sieved lactose monohydrate
D 200M	DMV Pharmatose® 200M milled lactose monohydrate
D 11SD	DMV SuperTab® 11SD spray-dried lactose monohydrate
D 21AN	DMV SuperTab® 21AN lactose anhydrous
HPMC	Hydroxypropylmethylcellulose
ChP	PHARMACEUTOPEDIA OF THE PEOPLE'S REPUBLIC OF CHINA (2010)
Cu	Content uniformity

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